AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1-200. (Cancelled)

201. (Currently Amended) A functional synthetic siRNA for interacting with a target mRNA of a target gene and silencing the target gene, the siRNA comprising:

a sense strand comprising:

a sense region;

a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

an antisense strand comprising an antisense region which is at least substantially complementary with the mRNA of the target gene and the sense region.

202. (Previously Presented) The siRNA of claim 201, wherein a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end.

203. (Currently Amended) The siRNA of claim 202, further comprising a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2'-OH ~~modification~~ and the first nucleotide of the antisense strand having a 2'-OH ~~modification~~.

204. (Cancelled)

205. (Currently Amended) The siRNA of claim 202 ~~204~~, wherein ~~the 2'-O-alkyl modification is a 2'-O-methyl modification for each of the first and second nucleotides of the sense and antisense strands, and~~ all nucleotides in the sense and antisense regions other than ~~the~~ first and second nucleotides of the sense and antisense strands have a 2'-OH.

206. (Currently Amended) The siRNA of claim 202, wherein the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification, wherein the 2' modification in the antisense region is selected from the group consisting of 2'-O-alkyl, 2'-deoxy, 2'-amine, 2'-alkyl, and 2'-fluoro.

207. (Previously Presented) The siRNA of claim 206, wherein the 2'-O-alkyl modification on the first and second nucleotides of the sense strand is a 2'-O-methyl modification and the 2' modification on the at least one nucleotide in the antisense region is a 2'-O-methyl modification.

208. (Previously Presented) The siRNA of claim 202, wherein all nucleotides in the sense and antisense regions other than the first and second nucleotides of the sense strand each have a 2'-OH.

209. (Previously Presented) The siRNA of claim 202, wherein a third nucleotide in the sense strand has a 2'-O-alkyl modification, the third nucleotide being immediately next to the second nucleotide from the 5' end of the sense strand.

210. (Cancelled)

211. (Currently Amended) The siRNA of claim 209 ~~210~~, wherein the 2'-O-alkyl modification is a 2'-O-methyl modification for the first, second, and third nucleotides of the sense strand ~~and antisense strands~~ and all nucleotides in the sense and antisense regions other than the first, second, and the third nucleotides of the sense and antisense strands have a 2'-OH.

212. (Cancelled)

213. (Previously Presented) The siRNA of claim 202, wherein the antisense strand has at least one phosphorothioate internucleotide linkage.

214. (Previously Presented) The siRNA of claim 202, wherein the antisense strand has at least one methylphosphonate internucleotide linkage.

215. - 219. (Cancelled)

220. (Previously Presented) The siRNA of claim 202, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

221. (Previously Presented) The siRNA of claim 220, wherein the 3' overhang has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

222. - 223. (Cancelled)

224. (Previously Presented) The siRNA of claim 202, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

225. (Previously Presented) The siRNA of claim 224, wherein the conjugate is cholesterol.

226. (Currently Amended) The siRNA of claim 225 ~~203~~, wherein the ~~further comprising at least one~~ conjugate molecule is coupled to the 3' end of the sense or antisense strand.

227. (Currently Amended) The siRNA of claim 226, wherein the conjugate is coupled to the sense strand ~~cholesterol~~.

228. (Currently Amended) A functional synthetic siRNA for interacting with a target mRNA of a target gene and silencing the target gene, the siRNA comprising:

a sense strand comprising:

a sense region;

a first nucleotide of the sense region ~~strand~~ closest to the 5' end of the sense region ~~strand~~ having a 2'-O-alkyl modification and being devoid of a phosphate at its 5' end; and

a second nucleotide of the sense region ~~strand~~ next closest to the 5' end of the sense region ~~strand~~ having a 2'-O-alkyl modification; and

an antisense strand comprising:

an antisense region which is at least substantially complementary with the mRNA of the target gene and the sense region;

a first nucleotide of the antisense strand closest to the 5' end of the antisense strand having ~~a 2'-O-alkyl modification and~~ a phosphate at its 5' end~~; and~~

~~a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2'-O-alkyl modification~~.

229. (Cancelled).

230. (Currently Amended) The siRNA of claim 228 ~~229~~, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

231. (Previously Presented) The siRNA of claim 230, wherein the antisense strand has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

232. (Currently Amended) The siRNA of claim 228 ~~229~~, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

233. (Previously Presented) The siRNA of claim 232, wherein the conjugate is cholesterol.

234. (New) A functional synthetic siRNA that silences a target gene, the siRNA comprising:

an inactive sense strand comprising at least one 2'-O-alkyl modification at the 5' end; and

an active antisense strand comprising an antisense region and a 5' terminal phosphate, said antisense region being at least substantially complementary with mRNA of the target gene.

235. (New) The siRNA of claim 234, wherein the inactive sense strand 2'-O-alkyl modifications consist of modified nucleotides at the 5' end.

236. (New) The siRNA of claim 234, wherein the 5' end consists of first and second nucleotides from the 5' terminus having 2'-O-methyl modifications.